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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,407	09/12/2001	Hugo R. Rosen	P-PM 4953	1602

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	//

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,407	ROSEN, HUGO R.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-34 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that a thorough search of Group I would reveal art that is relevant to Group II, hence a search of all the groups will not be burdensome. This is not found persuasive because the inventions of Group I and II are patentably distinct for reasons set forth of the record mailed on 2/11/03. A search of Group I would not be co-extensive with the search of Group II. Therefore, a search of all the groups in a single application would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 25-34 are withdrawn from consideration for being directed non-elected subject matter. Claims 1-24 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims are directed to a method of identifying a preferred liver transplantation donor by determining a preferred genotype at a polymorphic site that is associated with altered activity of a tumor necrosis factor (TNF). The claims encompass polymorphism at any sites of the genomic DNA that is related with altered activity of any TNF. The specification only discloses one polymorphism at –308 in the TNFα promoter that is associated with increased incidence of developing recurrent hepatitis C after liver transplantation. The specification also discloses that two polymorphisms in TNFβ, one in TNFC and NcoI site that is within the intron region of the TNFC gene are not associated with recurrent hepatitis C after liver transplantation. The specification fails to disclose additional

polymorphism in other regions of the genomic DNA that is associated with an altered TNF activity can be used as a determinant for preferred liver donor. As such, the structural functional relationship between a preferred genotype comprising polymorphism at a specific site that alters a TNF activity and the determinant of it being preferable as a liver donor is missing. The specification fails to describe the invention by a representative number of species by their complete structure nor other relevant identifying characteristics. Therefore, the inventors fail to describe the invention in such a way to reasonably convey an skilled artisan that the inventors had possession of the invention at the time of filing.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a preferred liver donor for transplantation to a recipient infected with hepatitis C virus comprising determining in the donor tissue the presence of a preferred genotype, wherein said genotype is polymorphism at nucleotide position –380 in the TNFα promoter, wherein a G is at said position, does not reasonably provide enablement for a method of identifying a preferred liver donor for any recipient by identifying a preferred genotype in said donor, wherein said genotype is a polymorphism at any site in the genome that is associated with altered activity of any tumor necrosis factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not

limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

Nature of the invention:

The nature of the invention is a method of identifying a preferred liver donor or selecting a preferred liver donor comprising determining in said individual the presence of a preferred genotype at a polymorphic site, wherein said preferred genotype is associated with altered activity of a tumor necrosis factor (TNF). The claims are further drawn to a specific polymorphic site within TNFα promoter that is considered as preferred donor type.

Breadth of the claim:

The broadest claim encompasses a method of identifying a preferred liver donor comprising determining in said individual the presence of a preferred genotype at any polymorphic site that is associated with altered activity of any of the TNF protein. Further, the claim encompasses a method of identifying preferred liver donor by determining the genotype of said donor regardless the status of recipient. The only enabled embodiment is a method of identifying a preferred liver donor for transplantation to a recipient infected with hepatitis C virus, comprising determining in the donor tissue the presence of a preferred genotype, wherein said genotype is polymorphism at nucleotide position –380 in the TNFα promoter, wherein a G is at said position. The specification does not provide sufficient support for other enablement of

the full scope of the claim. Therefore, the breadth of the claim is very broad and surpasses the teaching of the specification.

Amount of guidance in the specification:

The teaching of the specification is limited. The specification only provides sufficient support for a method of identifying a preferred liver donor for transplantation to a recipient infected with hepatitis C virus, comprising determining in the donor tissue the presence of a preferred genotype, wherein said genotype is polymorphism at nucleotide position –380 in the TNFα promoter, wherein a G is at said position. The specification provides an working example in which TNFα308.2 polymorphism is associated rapid, frequent, severe, recurrent of hepatitis C after liver transplantation to hepatitis C patients, whereas the patient received liver that has the wild type TNFα308.1 develop recurrent hepatitis C less frequently. The specification fails to teach other polymorphic site(s) in the genome, including those present in other TNF genes, that associates with altered TNF activity that correlated with a preferred donor type. On the contrary, the specification demonstrates in the working example that polymorphic alleles in other TNF genes such as TNFβ, TNFC and the Nco I site (in the intron of TNFC) do not correlate with the development of recurrence hepatitis C in patients after transplantation. Moreover, the specification fails to teach whether the TNF308.1 genotype that is preferred in recipient with hepatitis C is suitable donor type for recipient with other types of diseases. The scope of claims thus surpasses the guidance of the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

The state of art at the time of filing teaches multiple factors that affect successful outcome of liver transplantation, and patients/recipients with different disease have different risk factors for transplantation. For example, the development of EBV-PTLD, which represents a major complication after liver transplantation, is associated with using of immunosupression with tacrolimus and age at transplantation (see Guthery et al., page 990, 2nd col., 3rd paragraph). In patients with autoimmune disease, age is a risk factor because pediatric patients have increased risk to develop colitis after liver transplantation (see Heffron et al. abstract). Base on such teaching, whether a genotype that is preferred to recipient with hepatitis C can predict the success of liver transplantation to recipient with different disease is unpredictable. The specification only teaches a specific G-A mutation at nucleotide position –308 of TNFα gene increases risk of recurrent hepatitis C after transplantation to hepatitis C patients. As such, whether such mutation is associated with increased risk of other factors is unpredictable.

The state of art at the time of filing teaches a limited number of polymorphic sites within TNF genes. Such polymorphism sites including nucleotide position –308, -238 of the TNFα gene, Nco I site in TNFC (see Freeman et al. and Grove et al.). Freedman et al. teach that the polymorphism at Nco I site is associated with infection after liver transplantation (see abstract). Freedman et al. demonstrate that the presence of this Nco I site is associated with decreased TNFα production, and increased risk for developing infection in the first year after transplantation (see 1007, 2nd col., 2nd paragraph). Grove et al. teach that G to A mutation at nucleotide position –238 in TNFα promoter is associated with alcoholic steatohpatitis, whereas mutation of G to A at nucleotide position 308 is not (see page 145, 1st col., lines 8-12). Hohler et al. also teach that mutation at –238 is associated with chronic active hepatitis C infection (see

abstract). The specification teaches other than the TNFα308 mutation, other polymorphic sites in TNFα, β or C are not associated with increased risk of developing recurrent hepatitis C. The specification does not teach whether –238 mutation in TNFα is associated with increased risk of recurrent hepatitis C. Nor does the specification teach any other mutations within the TNF gene or outside of TNF gene that regulates TNF expression are associated with any type of risk factors relevant to liver transplantation. Therefore, whether a genotype associated with altered activity of any of the TNF protein is a relevant determinant for successful liver transplantation is unpredictable.

In view of the limited teaching of the specification and unpredictability in the art, the claimed invention is not enabled to its full scope. The specification only enables a method of identifying a preferred liver donor for transplantation to a recipient infected with hepatitis C virus comprising determining in the donor tissue the presence of a preferred genotype, wherein said genotype is polymorphism at nucleotide position –380 in the TNFα promoter, wherein a G is at said position. Without teaching from the specification, one of skilled in the art would have to engage in undue experimentation to practice the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-10, 13-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 8-10 and 20-22, the recitation of "a TNFα regulatory region" renders the claims indefinite because it is unclear what the term encompasses. In other words, does the term mean the region regulates TNFα function/expression or does it refer to a portion of TNFα that has regulatory activity of other protein?

Regarding claims 13-24, the word "material" renders the claims indefinite because it is unclear what the word encompasses. In other words, does it refer to an ID card, a clothing, tissue or DNA? As such, the metes and bounds of the claims cannot be established.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Celine Qian, Ph.D.
July 23, 2003